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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,601	08/24/2006	Sabine Balthasar	RO4304US (#90568)	8967

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EXAMINER	
WHEELER, THURMAN MICHAEL	
ART UNIT	**PAPER NUMBER**
1619	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/590,601	BALTHASAR ET AL.
	Examiner	Art Unit
	THURMAN WHEELER	1619

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14, 16-18 and 19-21* is/are pending in the application.

4a) Of the above claim(s) *6-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,16 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/25/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 2, 4-14, 16-18 and 19-21 are pending.

2. Claims 6-14, 17 and 18 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

3. Claims 19, 20 and 21 are newly added.

4. Herein, claims 1, 2, 4, 5, 16, 19, 20 and 21 are for further prosecution.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining differences between the prior art and claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.
> 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a),

the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The rejection of claims 1, 2, 4, 5 and 16 and newly added claims 19, 20 and 21 under 35 U.S.C. 103(a) as being unpatentable over Kreuter et al ((WO 02089776) where USP 2004/0131692 is used as English equivalent of PCT/EP2002/004735. Citations are to the English equivalent document, of record) and Paganelli (EPO 049607, 1992, of record) and Langer (European Journal of Pharmaceutics and Biopharmaceutics, 2000; received July 1999, IDS) is maintained.

Applicants claimed invention is directed to a carrier system for the cell-specific, intracellular enrichment of at least one pharmacologically active substance, wherein said carrier system is present in the form of protein-based nanoparticles to which biotinylated antibodies are bound, wherein said nanoparticles are based on at least one protein selected from the group consisting of gelatine and serum albumin, and said biotinylated antibodies are bound by forming a stable avidin-biotin complex with avidin which is covalently bound to the nanoparticles by bifunctional spacer molecules which are attached to reactive groups present on the surface of the nanoparticles; and wherein said antibodies enable a cell-specific attachment and cellular absorption of the nanoparticles.

Kreuter teaches nanoparticles having covalently coupled avidin, via which the functional protein biotinylated apolipoprotein E can be bound as is illustrated in FIG. 1. Avidin itself is a glycoprotein which is highly affine to biotin and is covalently bound via bifunctional spacer molecules to the thiol groups of the thiolated nanoparticles as exemplified in Fig. 1. By the covalent linkage of the avidin to the nanoparticles it is not only possible to bind biotinylated ApoE, which is necessary for the transport to the blood-brain barrier, but also to bind a variety of biotinylated molecules to the avidin-modified nanoparticles in a particularly efficient manner. For this purpose, pharmacologically or biologically active molecules are especially preferred [0013]. Accordingly, Kreuter teaches the biotinylated apolipoprotein E is bound via covalently coupled avidin (claim 6), and that at least one further biotinylated functional protein is bound via covalently coupled avidin (claim 7), where the functional proteins are antibodies (claim 5).

Further, Kreuter teaches to impart pharmacologic effects, pharmacologically or biologically active substances are incorporated in the nanoparticles, or they are bound by the nanoparticles, where the binding of the active agents may be performed covalently, with complex-formation via the avidin-

biotin system, as well as incorporatively or adsorptively ([0014]; claim 8; claim 9, claim 10).

Kreuter teaches amino groups, carboxyl groups, and hydroxyl groups located on the surface of the nanoparticles can be converted by suitable reagents to reactive thiol groups, where functional proteins are bound to the thiol group-modified nanoparticles via bifunctional spacer molecules having reactivity both to amino groups and free thiol groups [0011]. The functional proteins to be coupled to the nanoparticles are selected from the group comprising avidin, avidin derivatives, apolipoproteins such as apolipoprotein E, and also antibodies [0012].

Regarding claims 19 and 21, Kreuter teaches that Apolipoprotein E (ApoE) was biotinylated at 10°C, purified and then freeze dried [0040]. The freeze-dried ApoE was dissolved in water to which avidin-modified human serum albumin (HSA) nanoparticles was added and the mixture was incubated at room temperature to provide avidin-modified HSA nanoparticles comprising ApoE bound to the nanoparticles via the avidin-biotin system [0041-00045]. Thus, the biotinylated ApoE binds to the available binding sites on avidin that is covalently bound to the thiolated nanoparticles via a bifunctional spacer molecule (sulfo-MBS). One skilled in the art at the time of the invention

would have recognized that the available binding sites on avidin could be readily optimized using routine experimentation, e.g. varying the relative amounts of avidin and modified HSA nanoparticles that is used to prepare avidin-modified HSA nanoparticles. Thus, one skilled in the art at the time of the invention would have had a reasonable expectation of success of providing avidin-modified HSA nanoparticles wherein the nanoparticles have 2.4 binding sites that are available to form avidin-biotin complex by following the guidance provided by Kreuter. Moreover, in accordance with the teachings of Kreuter, one skilled in the art would have recognized that an antibody could also be used as a functional protein that is bound to the avidin-modified HSA nanoparticles to form a stable avidin-biotinylated antibody complex. Where the general conditions of a claim are disclosed in the prior art (as taught by Kreuter), it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454,456, 105 USPQ 233,235 (CCPA 1955).

Regarding claim 20, Kreuter teaches a purification method of functional protein comprises centrifuging and redispersing in purified water ([0036], [0037], [0039]).

Kreuter reference teaches that biotinylated antibodies are bound by an avidin-biotin complex *supra*. However, the Kreuter

reference does not explicitly embody using biotinylated monoclonal antibodies bound by a stable avidin-biotin complex.

Paganelli teaches a biotinylated monoclonal antibody, or biotinylated fragments thereof, specific to a tumour-associated antigen expressed by the tumor, wherein a protein of the avidin type binds to biotin. Furthermore, Paganelli teaches a biotinylated monoclonal antibody is administered to a patient, such that avidin is and subsequently administered that specifically binds to the biotinylated monoclonal antibody (col.2, lns.15-32; col.4, lns.21-40).

Langer teaches the preparation of avidin-labeled protein nanoparticles as carriers for biotinylated peptide nucleic acid. Langer teaches preparing protein nanoparticles followed by covalent linkage of avidin, wherein free sulfhydryl groups were introduced onto the surface of protein nanoparticles. The number of primary amino groups and sulfhydryl groups on the surface of the resulting particles was quantified with site- specific reagents. Further, avidin was attached to the surface of the thiolated nanoparticles via a bifunctional spacer. Biotinylated peptide nucleic acid (PNA) was effectively coupled to the nanoparticles by complex formation with the covalently attached avidin (see Fig. 1).

It would have been obvious to one skilled in the art at the time of the invention to modify the nanoparticles as taught by Kreuter to include biotinylated monoclonal antibodies that are complexed with avidin, because Kreuter teaches that a variety of biotinylated functional proteins can be complexed to the avidin-modified nanoparticles in an efficient manner, which specifically includes biotinylated antibodies. Furthermore, Paganelli explicitly teaches that a biotinylated monoclonal antibody can be complexed to a protein of the avidin type. One would have been motivated to provide a biotinylated monoclonal antibody, since it can be used to specifically target a tumour-associated antigen expressed by a tumor as taught by Paganelli. Additionally, one skilled in the art would have recognized that other biotinylated molecules such as peptide nucleic acids could also be complexed to nanoparticles via an avidin complex as taught Langer. Thus, one skilled in the art at the time of the invention would have recognized that a biotinylated monoclonal antibody as taught by Paganelli could also be complexed to the avidin-modified HSA nanoparticles as taught by Kreuter for the purpose of targeting the nanoparticle to a specific tumor site.

One skilled in the art at the time of the invention would have had a reasonable expectation of success to provide a

nanoparticle as claimed by Applicants by following the teachings of Kreuter, Paganelli and anger, as a whole.

Accordingly, the claimed invention of instant claims 1, 2, 4, 5 and 16, 19, 20 and 21 were prima facie obvious to one skilled in the art at the time of the invention was made especially in the absence of evidence to the contrary.

Response to Arguments

6. Applicants argue that Kreuter fails to teach nanoparticles having biotinylated antibodies bound to avidin moieties which are coupled to the nanoparticle surface via bifunctional spacer molecules. Kreuter does not teach using biotinylated antibodies.

Applicants' arguments filed 25 April 2011 have been fully considered but they are not persuasive, because Kreuter teaches biotinylated functional proteins are bound via covalently coupled avidin, where the functional proteins are antibodies (claim 5 and claim 7 as discussed above).

Applicants argue that the teaching of the complex by Paganelli is merely speculative. Paganelli teach certain biochemical reactions that are supposed to take place inside a human or animal body system upon sequential administration of reagents a), b) and c). Reagent a) is a biotinylated monoclonal antibody, reagent b) is a protein of the avidin type and reagent c) is a biotin conjugated with an agent, e.g. radioisotope. It is further submitted that since the alleged reactions between biotinylated antibody and avidin take place inside the human or animal body, and since a "stable

avidin complex" was neither positively observed nor produced in an isolated form (in vitro), it is respectfully submitted that it remains purely speculative whether such complexes were ever obtained by following the in vivo procedure described by Paganelli. Furthermore, since biotin is generally known to be a normal (and vital) component of the blood the Applicants submit that it is questionable whether "protein of avidin type" when administered in accordance with the teachings of Paganelli will form complexes with the biotinylated antibodies since the patient's serum already contains biotin. It would be expected then that the serum which already contains biotin would bind to the biotin binding sites of the "protein of avidin type" (reagent b)), thus blocking these binding sites and preventing the alleged complex formation with biotinylated antibodies.

Applicant's arguments have been fully considered but they are not persuasive, because the Paganelli reference was relied upon to teach a biotinylated monoclonal antibody. Accordingly, one skilled in the art at the time of invention would have recognized that biotinylated monoclonal antibodies could be used to specifically target a tumour-associated antigen expressed by a tumor as taught by Paganelli. Further, one skilled in the art would have recognized that these biotinylated monoclonal antibodies could be used to form stable avidin-biotin complex with the avidin-modified HSA nanoparticles as taught by Kreuter.

Moreover, it is well established in the art that avidin and biotin form a stable avidin-biotin complex.

Furthermore, Paganelli addresses the issue concerning biotin in the serum. Paganelli teaches that at an appropriate

time after administration, the only extracellular biotins are those anchored to the tumour cells, whilst all the biotin naturally present in the human body and the exogenous biotin conjugated with that fraction of the monoclonal antibodies which, after administration, reached nonspecific sites are located within cells and hence are no longer directly accessible to extracellular fluids (see page 2, column 1, lines 53-58 to column 2, lines 1-4).

Particularly, Paganelli teaches that the biotinylated monoclonal antibodies are stable and are therefore suitable for commercial preparations in large batches according to known techniques. Thus, one skilled in the art at the time of the invention would have been motivated to use the biotinylated monoclonal antibodies because due to their stability as taught by Paganelli.

Conclusions

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this

action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thurman Wheeler whose telephone number is (571)270-1307. The examiner can normally be reached on 9:00 a.m.-5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Blanchard can be reached (571)272-0827. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

T.W.

/Anne M. Gussow/
Primary Examiner, Art Unit 1643